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DATA EVALUATION REPORT VII

STUDY TYPE: 90-day subchronic feeding - dog TOX. CHEM. NO: 316

ACCESSION NUMBER: not given MRID NO: 92165

TEST MATERIAL: 2,4-DB

SYNONYMS: 4-(2,4-dichlorophenoxy)butyric acid, 2,4 DB Acid

STUDY NUMBER(S): Project No. 656-110

SPONSOR: The Chipman Chemical Co., Inc.

TESTING FACILITY: Hazleton Laboratories, America Inc.

TITLE OF REPORT: 13-Week Oral Administration - Dogs

AUTHOR(S): Holsing, G. C., Voelker, R. W. Jr.

REPORT ISSUED: 11/05/69

CONCLUSIONS:

This study was reviewed by D. Ritter (memo dated 11/11/71, see attached). This reviewer generally agrees with the conclusions given at that time, although the statement: "A no-effect level lies between 316 and 1000 ppm in the diet for thirteen weeks in dogs." would now be written to state that 316 ppm (equivalent to 7.9 mg/kg/day) is the NOEL and 1000 ppm (equivalent to 25 mg/kg/day) is the LEL. The study was not given a core classification in the review of 11/11/71; after examining the report this reviewer concludes that it is core minimum.

Classification: CORE MINIMUM

A. MATERIALS AND METHODS:

1. Test Compound:

Chemical name: 2,4-DB Acid (technical), 98.5% active.
Description: Pale brown granular material with a disagreeable odor.
Batch #: lot no. 811012.

2. Test Animals:

Species and Strain (Sexes): Male and female purebred beagles.
Age: "Young adult"
Weight(s): 6.6 - 11.9 kg at study initiation
Source: not reported

Additions to the previously submitted review:

1. Procedures:

From the way the study is reported, it appears that group 5, the lowest dose group (2.5 mg/kg/day in capsules throughout the 13-week study period) was added several weeks after the rest of the study was underway. The other groups received the test material in their diets during the first two weeks (group 1, control, 0 ppm; group 2, 316 ppm; group 3, 1000 ppm; group 4, 3160 ppm) and then by equivalent dosage in gelatin capsules (0, 8, 25 and 80 mg/kg/day respectively) 7 days/week for the remainder of the study period.

2. Results:

It is noted that blood and urinalysis parameters, as well as terminal organ weights and organ-to-body weight ratios were not statistically analyzed. However, after examining the values for these findings, this reviewer has come to the conclusion that with statistical analyses there would be no major changes in the conclusions of the original review.

2. Subacute Toxicity

a. 13 week Oral Administration to Dogs

1. Methods

Groups of 4 Male and 4 Female beagles were given 2,4-DB (acid 100% active ingredient).

0,100,316,1000 or 3160 ppm in the diet (first two weeks) and 2.5, 8,25 or 80 mg/kg/ day by capsule for the remainder of the test period; these latter levels are equivalent to the dietary levels.

Appearance, appetite, elimination, toxic signs; weekly body weight and food consumption were noted.

Clinical laboratory studies were performed initially, at 4 weeks and at termination, and consisted of:

Blood:

Hct, Hb, WBC's RBC's % Differentials, Prothrombin time, FBS, BUN, Total Protein, Serum Dilirubin, Serum Albumin, Na, K, Ca, CO_2, BSP, SGOT, SGPT, SAP and serum electrophoresis.

Urine:

Sp. Grav., pH, Glucose, Ketones, Total protein, bilirubin, and microscopic formed elements.

Terminal studies of those animals surviving till the end or until killed in extremis included gross and histological examination of representative tissues and organs from all animals.

Thyroid GI	Adrenal GI
Heart	Gallbladder
Spleen	Liver
Kidney	Stomach
Pancreas	Sm. Intestine
Lge. Intestine	Urinary Bladder
Mesnt. Lymph Nde.	Gonad
Marrow	Unusual lesions

Weights were obtained on thyroid gl. heart, liver, spleen, kidney, adrenals and testes in the control, 316 ppm and 1000 ppm animals; selected grossly abnormal tissues from group on 3160 ppm; and the liver and kidneys only of the 100 ppm group.

2. Results:

Physical condition and Mortality - One dog died and the remaining seven were killed in extremis in the third week on the 3160 ppm dose. Physical condition of these animals was very poor but the toxicity was of a generalized nature: diarrhea, depression, discoloration of mucous membranes; weight loss was widespread in this group.

Animals on the 1000 ppm dose exhibited much the same symptoms; 2 male and 2 females had to be killed prior to termination.

Weight losses were seen in seven of the eight animals. Physical condition of the 316 and 100 ppm groups was comparable to controls.

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Hematology finding were negative for effect of 2,4-DB at 0,100, 316 and 1000 ppm in the diet; the 3160 ppm group was terminated in extremis at the third week.

Adverse hematology findings were limited to the 3160 and 1000 ppm groups and included decreased HCT, Hb, RBC's and increased WBC's in the 1000 ppm group by week 13. (The 3160 ppm group suffered 100% mortality by the 3rd week).

Clinical chemistry findings were also confined to the two highest groups and consisted of increased SAP, BUN, Bilirubin, SGOT, SGPT, and BSP retention times; reduced values included serum Na, Ca, CL and albumin. These alterations are of questionable significance since they are minimal, and not outside the normal ranges for dogs.

Urinalysis was not remarkable for toxic effect other than in the sacrificed high-dose dogs which demonstrated occult blood (1 dog), increased bilirubin, and urinary RBC's.

Those gross Pathological changes seen in the 1000 and 3160 ppm dogs consisted of icterus or a gray discoloration of sclera, oral musoca and connective tissue; reddened lymph-node medullae, distended gallbladders, pale livers, eye discharges, lung froth, discolored kidney, gastric muscosal petechiae, subepicardial hemorrhages and altered large intestine mucosa.

Organ/body weight ratio alterations were confined to the 100 and 3160 ppm levels and consisted of increases for; liver, spleen, kidney, adrenals and testes.

Microscopic pathology showed hemorrhage and edema of most tissues and organs; hepatocytic necrosis, renal dilation of tubules, aspermatogenesis and altered ovarian, thyroid and pancreatic function at the 3160 and 1000 ppm levels, while the lower-dose dogs were essentially normal.

3. Conclusions:

A no-effect level lies between 316 and 1000 ppm in the diet for thirteen weeks in dogs.